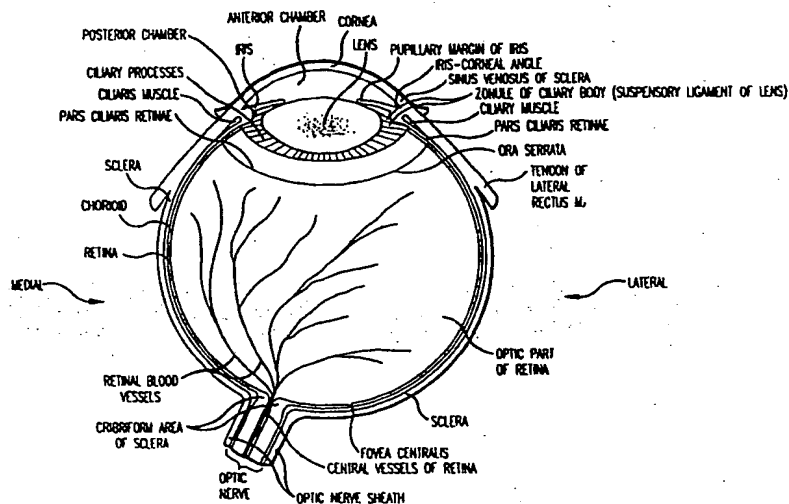


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(54) Title: CONTROLLED RELEASE OF PHARMACEUTICALS IN THE ANTERIOR CHAMBER OF THE EYE



(57) Abstract

The present invention relates to compositions which maintain the structural integrity of the anterior chamber of the eye during ophthalmologic surgery, thereby protecting the tissues that form and line the anterior segment from potential damage and simultaneously providing sustained delivery of pharmaceuticals, including miotic, mydriatic or anesthetic agents.

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CONTROLLED RELEASE OF PHARMACEUTICALS
IN THE ANTERIOR CHAMBER OF THE EYE

SPECIFICATION

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1. INTRODUCTION

The present invention relates to compositions, comprising a viscoelastic polymer and a miotic or mydriatic agent, which maintain the structural integrity of the anterior chamber of the eye during ophthalmological surgery, thereby protecting the tissues that form and line the anterior segment from potential damage and simultaneously providing sustained delivery of a miotic or mydriatic agent. The present invention also provides for compositions wherein sustained release of a miotic or mydriatic agent is mediated by microcapsules or copolymer micelles. The present invention further relates to compositions comprising a viscoelastic polymer-anesthetic complex which maintain the integrity of the anterior chamber of the eye while providing sustained delivery of a non-infiltrative anesthetic.

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2. BACKGROUND OF THE INVENTION

Maintaining the integrity of the anatomic components of the eye facilitates the delicate manipulations, performed within small areas, of ophthalmological surgery.

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One component which may be controlled is the anterior chamber of the eye. As shown in Figure 1, the anterior chamber is located between the cornea and the iris. Just posterior to the iris is the lens, which is interposed between the anterior chamber and the larger vitreous chamber, filled with vitreous humor. Maintaining the structural integrity of the anterior chamber minimizes the risk that the endothelium and/or the iris will be damaged during surgery. The introduction of viscoelastic materials, such as sodium hyaluronate, chondroitin sulfate, hydroxypropyl

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methylcellulose, and methylcellulose, into the anterior chamber prevents the chamber from collapsing during surgery.

Another component that may be controlled is pupil size. During cataract surgery, it is desirable that the pupil is dilated, so that access to the lens is simplified and the insertion of a posterior chamber implant is facilitated. A variety of mydriatic drugs, such as atropine (a cholinergic blocker), phenylephrine (an adrenergic stimulator), and prostaglandin inhibitors have been used in this regard, and have hitherto predominantly been administered via external application.

Conversely, in refractive implants and secondary aphakic implants, a smaller ("miotic") pupil is desirable, in order to reduce iris trauma, avoid anterior synechias, prevent iris tucking, and facilitate appropriate positioning of the implant. Externally applied pilocarpine and carbachol (cholinergic stimulators), and physostigmine, demecarium bromide, echothiophate iodide, and isofluorophate (cholinesterase inhibitors) have been used for this purpose.

During surgery, however, and in the open eye, the efficacy of topical medication is reduced. Dilution and runoff preclude a continued high dose of effective medication. Even the direct introduction of miotic agents such as acetylcholine chloride or carbachol do not provide long term effects and often require frequent repeated administration into the open eye.

Previous attempts to achieve long-term maintenance of effective drug levels have employed sustained drug delivery technology, using systemic or transdermal administration, or the positioning of a bioerodible drug delivery device external to the eye. Such methods have been used primarily to control intraocular pressure in glaucoma patients. However, prior to the present invention, no method has been devised which combines sustained mydriatic or miotic drug delivery with maintenance of the structural integrity of the anterior chamber.

Local anesthesia has been the mainstay of ocular surgery. Topical agents have been employed to anesthetize the cornea and conjunctiva, and infiltrative anesthesia has been used to create sensory anesthesia and motor akinesia necessary for eye surgery. When injected into the muscle cone, these agents anesthetize the ciliary ganglion, afferent nerves and the motor innervation to the extra-ocular muscles.

However, retrobulbar hemorrhage, caused by muscular or vascular trauma, is a potential complication of this form of anesthesia which may preclude performing the surgical procedure. More rarely, perforation of the globe, optic nerve damage, and even total visual loss can occur. Further, systemic absorption of anesthetic may cause
5 seizures, respiratory problems, and even death.

To avoid these potential complications, infiltration anesthesia has been carried out with subtenons injections, subconjunctival injections and direct infiltration of one or more extra-ocular muscles. This approach, while somewhat more cumbersome, has reduced the potential anesthetic-related complications, but carries its
10 own risks, such as chemosis, subconjunctival or subtenons hemorrhage and incomplete sensory and motor anesthesia, particularly during ciliary body and iris manipulation.

With the advent of extracapsular cataract surgery as a primary approach, a different set of anesthesia requirements has evolved. The need for motor
15 anesthesia has been reduced, as instrumentation utilized during the surgical procedure may be used to fixate the globe. The need for bridge sutures, whose placement can be painful, has been virtually eliminated. What remains is the requirement to prevent pain, particularly that induced by iris manipulation. Intracameral anesthetics directly placed into the anterior chamber have been used in this context.

20 The use of intracameral anesthetic may be effective, but may require frequent instillation of anesthetic, particularly at times when the surgeon is involved in other steps and may not be able to add additional material with safety. Further, conventional anesthetic solutions typically exit the eye promptly, through the surgical site, through normal outflow channels, and through iris and ciliary body surfaces.

25 What would be desirable is a sustained release system which maintains anesthetic presence and simultaneously reduces the surge effect of intracameral placement and immediate loss through the aforementioned pathways. What would be further desired is a drug delivery system that achieves duration of anesthetic release, a more uniform release of the anesthetic over time, and control of osmotic pressure
30 associated with the equilibrium formed between the ions of the anesthetic and the existing ions in the eye fluids.

3. SUMMARY OF THE INVENTION

The present invention relates to compositions which may be used to maintain the structural integrity of the anterior chamber of the eye and to provide sustained release of a miotic or mydriatic agent and/or an anesthetic compound. In various embodiments of the invention, compositions of the invention comprise a viscoelastic polymer, wherein sustained release of a miotic, mydriatic and/or anesthetic agent is mediated by ionic interactions. In further embodiments of the invention, sustained release of a miotic, mydriatic and/or anesthetic agent is mediated by microcapsules or copolymer micelles. In particular embodiments, the compositions of the invention may be used to provide both rapid release of miotic, mydriatic and/or anesthetic agent as well as slower, sustained release.

4. BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1. Clemente, 1978, in "Anatomy", Lea and Fibiger, Philadelphia, fig. 501.

FIGURE 2. Dilution effect of miotic or mydriatic agents in the anterior chamber of the eye caused by the normal turnover rate of aqueous humor, in the presence or absence of viscoelastic polymer-drug complex. Curve A represents unbound drug = 0.0500 moles/liter in physiological saline; Curve B represents unbound drug = 0.025 moles/liter plus viscoelastic polymer-drug complex = 0.0500 equivalents/liter in physiological saline; and Curve C represents viscoelastic polymer-drug complex = 0.100 equivalents/liter in physiological saline.

FIGURE 3. Dilution effect of anesthetic agent lidocaine in the anterior chamber of the eye caused by the normal turnover rate of aqueous humor, in the presence or absence of anesthetic-viscoelastic polymer complex: curve A represents unbound anesthetic = 0.0085 mole/liter in physiological saline; curve B represents unbound anesthetic = 0.0049 mole/liter plus anesthetic-viscoelastic complex = 0.150 equivalents/liter in physiological saline; and curve C represents anesthetic-viscoelastic polymer complex = 0.348 equivalents/liter in physiological saline.

5. DETAILED DESCRIPTION OF THE INVENTION

For clarity of presentation, and not by way of limitation, the detailed description of the invention is divided into the following sections:

- (1) viscoelastic polymers;
- (2) miotic agents;
- (3) mydriatic agents;
- (4) anesthetic agents;
- (5) compositions of the invention; and
- (6) methods for using the compositions of the invention.

5.1. VISCOELASTIC POLYMERS

The present invention provides for compositions comprising viscoelastic polymers, including but not limited to the anionic salt and free acid forms of viscoelastic polymers hyaluronic acid (hyaluronate), chondroitin sulfate, dermatan sulfate, carboxymethylcellulose, heparan sulfate, heparin, keratan sulfate, carboxymethylhydroxypropylcellulose, carboxymethylhydroxyethylcellulose, cellulose sulfate, cellulose phosphate, carboxymethylguar, carboxymethylhydroxypropylguar, carboxymethylhydroxyethylguar, xanthan gum, gellan gum, welan gum, rhamosan gum, agarose, alginates, furcellaran, pectins, gum arabic, gum tragacanth, carrageenans, starch phosphates, starch succinates, glycoaminoglycans, polysaccharides, polypeptides, anionic polysaccharides, anionic proteins and polypeptides, anionic polyacrylamide, anionic poly-N-vinylpyrrolidone, anionic polydimethyl acrylamide, polymers and copolymers of acrylamide, N-vinylpyrrolidone, dimethylacrylamide, acrylic acid, methacrylic acid, maleic anhydride, sodium vinyl sulfonate, 2-acrylamido-2-methyl-propanesulfonic acid, vinylphosphonic acid, and 2-methacryloyloxyethylsulfonic acid. The foregoing compounds, in their non-ionized free-acid forms, may function as acidic polymers; in their ionized forms, the compounds may function as polymeric anions.

The viscoelastic polymers of the invention range in molecular weight from 50,000 to 8,000,000 daltons, depending on the polymer of choice, of commercially available polymers that have been approved for ophthalmic use. For

example, an average molecular weight of from 1,000,000 to 5,000,000 daltons is commonly used for sodium hyaluronate, whereas an average molecular weight of greater than 80,000 daltons is normally used for hydroxypropylmethylcellulose. For example, a molecular weight commonly used for sodium hyaluronate in

5 ophthalmological surgery is 5,000,000 daltons. The concentration of viscoelastic polymer may vary from 1 mg/ml to 60 mg/ml, and preferably from 5 mg/ml to 30 mg/ml. The viscosity of the viscoelastic polymer may vary from 1000 centistokes to 60,000 centistokes, and preferably from 2,500 centistokes to 5,500 centistokes for hydroxypropylmethylcellulose and from 20,000 centistokes to 40,000 centistokes for

10 sodium hyaluronate. Such viscosities not only enable the introduction of the polymer into the eye by injection or extrusion, but also are viscous enough to remain within the anterior chamber (that is to say, will not run off easily), maintain its structural integrity, and permit easy withdrawal. Furthermore, the viscoelastic polymers of the invention are water soluble and can be eluted with time.

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5.2. MIOTIC AGENTS

The present invention provides for compositions comprising miotic agents including, but not limited to, pilocarpine, isopilocarpine, pilocarpine hydrochloride, pilocarpine nitrate, isopilocarpine hydrochloride, isopilocarpine nitrate, carbachol, physostigmine, physostigmine sulfate, physostigmine sulfite, demecarium

20 bromide, ecothiophate iodide and acetylcholine chloride. Preferred agents are members of the pilocarpine and isopilocarpine family of compounds.

The miotic agents of the invention may be utilized in either neutral or charged, cationic form, depending on the nature of the sustained drug delivery to be provided by the composition. Of the foregoing list, agents that are considered basic

25 include: pilocarpine, isopilocarpine, and physostigmine; agents that are considered hydrophobic include: pilocarpine, isopilocarpine, and physostigmine; and agents that are considered cationic include demecarium bromide, ecothiophate iodide, pilocarpine hydrochloride, pilocarpine nitrate, isopilocarpine hydrochloride, isopilocarpine nitrate, carbachol, physostigmine sulfate, acetylcholine chloride and physostigmine sulfite.

5.3. MYDRIATIC AGENTS

The present invention provides for compositions comprising mydriatic agents including, but not limited to, atropine, atropine sulfate, atropine hydrochloride, atropine methylbromide, atropine methylnitrate, atropine hyperduric, atropine N-oxide, phenylephrine, phenylephrine hydrochloride, hydroxyamphetamine, hydroxyamphetamine hydrobromide, hydroxyamphetamine hydrochloride, hydroxyamphetamine iodide, cyclopentolate, cyclopentolate hydrochloride, homatropine, homatropine hydrobromide, homatropine hydrochloride, homatropine methylbromide, scopolamine, scopolamine hydrobromide, scopolamine hydrochloride, scopolamine methylbromide, scopolamine methylnitrate, scopolamine N-oxide, tropicamide, tropicamide hydrobromide, and tropicamide hydrochloride. Preferred agents are members of the atropine family and phenylephrine family of compounds.

The mydriatic agents of the invention may be utilized in either neutral or charged, cationic form, depending on the nature of the sustained drug delivery to be provided by the composition. Of the foregoing list, agents that are considered basic include: atropine, phenylephrine, hydroxyamphetamine, cyclopentolate, homatropine, scopolamine, and tropicamide; agents that are hydrophobic include atropine, phenylephrine, hydroxyamphetamine, cyclopentolate, homatropine, scopolamine, and tropicamide; and agents that are considered cationic include atropine sulfate, atropine hydrochloride, atropine methylbromide, atropine methylnitrate, atropine hyperduric, atropine N-oxide, phenylephrine hydrochloride, hydroxyamphetamine iodide, hydroxyamphetamine iodide, hydroxyamphetamine hydrobromide, cyclopentolate hydrochloride, homatropine hydrobromide, homatropine hydrochloride, homatropine methylbromide, scopolamine hydrobromide, scopolamine hydrochloride, scopolamine methylbromide, scopolamine methylnitrate, scopolamine N-oxide, tropicamide, and tropicamide hydrobromide.

5.4. ANESTHETIC AGENTS

The present invention provides for compositions comprising anesthetic agents that are cationic in charge (cationic amine salts) or potentially cationic in

charge (uncharged amino groups), such agents comprising lidocaine, proparacaine, tetracaine, phenacaine, naepaine, lidocaine, cocaine, betoxycaine, bupivacaine, butacaine, butanilcaine, butoxycaine, carticaine, cyclomethycaine, dibucaine, dimethocaine, etidocaine, formcaine, hexylcaine, hydroxytetracaine, leucinocaine, 5 mepivacaine, meprylcaine, metabutoxycaine, myrtecaine, octacaine, orthocaine, oxethazine, parethoxycaine, piperocaine, piridocaine, pfilocaine, procaine, propanocaine, propipocaine, propoxycaine, pseudocaine, pyrrocaine, ropivacaine, tolylcaine, tricaine and trimecaine. Preferred agents are lidocaine, proparacane and tetracaine.

10 The anesthetic agents of the invention may be used in their neutral, uncharged form or their charged, cationic form, depending on the sustained drug delivery method to be provided by the composition. Of the foregoing list, all neutral compounds contain primary amino groups, secondary amino groups, and/or tertiary amino groups, while the charged, cationic groups contain hydrochloride salts, nitrate 15 salts, sulfate salts, mesylate salts, butyrate salts, acetate salts, tartrate salts, citrate salts, or phosphate salts of said amino groups by the protonation of the primary, secondary, or tertiary amino groups with the respective acids. Neutral amino anesthetic agents include lidocaine, tetracaine, proparacaine, naepaine, cocaine, phenacaine, betoxycaine, bupivacaine, butacaine, butanilcaine, butoxycaine, 20 carticaine, cyclomethycaine, dibucaine, dimethocaine, etidocaine, formcaine, hexylcaine, hydroxytetracaine, leucinocaine, mepivacaine, meprylcaine, metabutoxycaine, myrtecaine, octacaine, orthocalne, oxethazine, parethoxycaine, piperocaine, piridocaine, prilocaine, procaine, propanocaine, propipocaine, propoxycaine, pseudocaine, pyrrocaine, ropivacaine, tolylcaine, tricaine, and 25 trimecaine. Charged cationic anesthetic agents are prepared from the above by protonation with acids such as hydrochloric acid, sulfufic acid, nitric acid, phosphoric acid, methylsulfonic acid, butyric acid, acetic acid, citric acid, and tartaric acid.

5.5. COMPOSITIONS OF THE INVENTION

The present invention provides for compositions which provide 30 sustained release of miotic, mydriatic, and/or anesthetic agents, as described above, in

which release of the agent is mediated by (1) ionic (including acid-base) interactions; (2) microcapsules; or (3) copolymer micelles. The compositions also provide a means for maintaining the structural integrity of the anterior chamber of the eye.

In a first set of nonlimiting embodiments, the present invention provides for compositions in which the sustained release of miotic or mydriatic agent is achieved through ionic interactions between the agent and a viscoelastic polymer. In particular embodiments, a composition may comprise an anionic viscoelastic polymer and a cationic miotic or mydriatic agent, in which case the cationic agent of the composition, when placed in the eye, may be released by displacement with endogenous sodium or potassium ions, or other naturally occurring cations. In one specific, nonlimiting embodiment, the anionic viscoelastic polymer acid may be sodium hyaluronate, and the cationic agent may be the mydriatic agent atropine sulfate, where, in the preparation of the composition, sodium sulfate (and bisulfate) are removed by using an excess of the atropine sulfate in the presence of a lesser amount of sodium hyaluronate followed by dialysis. This process may be repeated several times to prepare a high purity of atropine hyaluronate. In another specific, nonlimiting embodiment, the anionic viscoelastic polymer may be chondroitin sulfate and the cationic agent may be the miotic agent pilocarpine, which may be combined by interacting sodium chondroitin sulfate with pilocarpine hydrochloride. In yet another specific, nonlimiting embodiment, an ion exchange interaction between sodium hyaluronate and phenylephrine hydrochloride can be effected, yielding phenylephrine hyaluronate.

In a second, related set of nonlimiting embodiments, the present invention provides for compositions in which the sustained release of miotic or mydriatic agent is achieved through ionic acid-base interactions between the agent and a viscoelastic polymer. In particular embodiments, a composition may comprise an acidic viscoelastic polymer and a basic miotic or mydriatic agent, in which case the composition, when placed in the approximately pH neutral environment of the eye, will provide a relatively slow release of the miotic or mydriatic agent by ionic displacement of the drug from existing cations. In one specific, nonlimiting embodiment, the acidic viscoelastic polymer acid may be hyaluronic acid, and the

basic agent may be the mydriatic agent atropine. When these two compounds are combined in the composition, the polymeric salt atropine hyaluronate may be formed. In another specific, nonlimiting embodiment, hyaluronic acid may be interacted with the basic miotic drug pilocarpine in water at a temperature range of 5 to 50°C

5 (wherein the pilocarpine becomes protonated by the polyacid and is rendered a salt of the viscoelastic polymer), followed by dialysis or ultrafiltration to remove unreacted pilocarpine. The resulting pilocarpine hyaluronate composition may then, alternatively, either be sterilized and adjusted to the appropriate pH and osmolality for use (for example, and not by way of limitation, where the pH range is between about

10 6.8 and 7.8, preferably between 7.2 and 7.4, and the osmolality is 285 ± 55 mOsm/kg and preferably between 290 and 320 mOsm/kg), or may be recovered by drying *in vacuo* or by lyophilization. In yet another specific, nonlimiting embodiment of the invention, hyaluronic acid may be interacted with the mydriatic agent phenylephrine in aqueous solution, using an excess of phenylephrine, followed by dialysis, yielding

15 phenylephrine hyaluronate.

In a nonlimiting example relating to the sustained release of a miotic or mydriatic agent from the anterior chamber of the eye, Figure 2 depicts three representative conditions using an aqueous humor volume of 310 microliters and an aqueous humor turnover rate of 1.5 microliters per minute (Schoenwald, 1993,

20 "Pharmacokinetics in Ocular Drug Delivery" (Chapter 10) in Biopharmaceuticals of Ocular Drug Delivery, CRC Press, Inc., Boca Raton, Fl.). Units for unbound drug are given in moles per liter, and units for viscoelastic polymers are given in units of equivalents per liter, which would describe any viscoelastic polymer with any miotic or mydriatic drug.

25 In Figure 2, curve A represents unbound drug, wherefor the initial concentration of 0.0500 moles/liter is diminished to 0.0084 moles/liter after 6 hours of dilution in the eye, caused by the turnover rate of aqueous humor. Curve B of Figure 2 represents a combination of unbound drug (no viscoelastic polymer present) and ion-complexed (bound) drug-viscoelastic polymer. In this curve, the viscoelastic

30 polymer-drug complex has a predicted cooperative binding constant of 5×10^{-2} (Hayakawa et al., 1983, Macromolecules 16:1642). This value was determined for

carboxymethylcellulose (as a model anionic viscoelastic polymer) with a hydrophilic cation of dodecyltrimethylammonium ion. From curve B it may be seen that, with an initial concentration of unbound drug of 0.0500 moles per liter, at 6 hours of aqueous humor turnover, 0.0340 moles per liter of medicament remains in the anterior chamber. This final concentration is more than 4-fold greater than the final concentration of unbound drug observed after 6 hours.

Curve C of Figure 2 represents ion-complexed (bound) drug-viscoelastic polymer, wherein the initial concentration of 0.100 equivalents per liter (producing an equilibrium initial concentration of 0.500 moles per liter of unbound drug) is reduced to 0.0354 moles per liter after 6 hours of duration in the eye, caused by the turnover of aqueous humor. This final concentration is more than 4 times greater than the final concentration of unbound drug, and slightly greater than that of Curve B. In this curve, the viscoelastic polymer-drug complex has a predicted cooperative binding constant of 5×10^{-2} (Hayakawa et al., 1983, *Macromolecules* 16:1642).

Thus, from Figure 2 it may be seen that two conditions of ion-complexed miotic or mydriatic drug/polymer complex clearly demonstrate the effect of sustained release of drug with time, as compared to unbound drug, in the anterior chamber of the eye.

In a third set of nonlimiting embodiments, the present invention provides for compositions which comprise microcapsules that are soluble or swellable in aqueous media and preferably biodegradable, which themselves comprise miotic or mydriatic agent, wherein the agent may be eluted with time as the microcapsule slowly dissolves, disintegrates, or swells. Typically, such microcapsules may desirably be smaller than the wavelength of light in order to prevent light scattering and impaired vision. In this procedure the agent of choice is incorporated into the microcapsule during formation of the microcapsule. Since the viscosity of microcapsules is typically low, a viscoelastic polymer may be added to maintain the anterior chamber.

Soluble microcapsules may be derived from inherently biodegradable polymers, such as poly-DL-lactide or poly-DL-lactide-co-glycolide, which, in dry

form, may be made into microcapsules containing an appropriate agent (Clarke et al., 1994, Polymer Preprints 35(2):73). Alternatively, soluble microcapsules may be derived from pH sensitive polymers, where a change in pH can cause expansion of the microcapsule, leading to a sustained release drug delivery system. An example of such a pH-sensitive polymer is poly(L)-lysine-alt-terephthalic acid, which, at pH values greater than 6, expands (Makino et al., 1994, Polymer Preprints 35: 54).

Biodegradable microcapsules containing miotic or mydriatic agent may be prepared using polymers, such as polylactide or polylactide-co-glycolide, that decompose after a period of time.

10 In a fourth set of nonlimiting embodiments, the present invention provides for compositions which comprise soluble copolymer micelles comprising a miotic or mydriatic agent, wherein the micelles comprise a hydrophilic and a hydrophobic portion, and the agent (in its uncharged form) is absorbed into the hydrophobic portion of the copolymer micelle (Arca et al., 1994, Polymer Preprints 35: 71). At equilibrium, a hydrophobic drug, such as phenylephrine, may be expected to reside both inside and outside the copolymer micelle. When the preparation is placed in the anterior chamber of the eye, as the exterior agent is removed, the interior agent may be slowly released. Such copolymer micelles may preferably be hydrophilic-hydrophobic or hydrophilic-hydrophobic-hydrophilic in character.

20 Preferably, the hydrophilic blocks are derived from ethylene oxide and the hydrophobic blocks from propylene oxide (ethylene oxide-propylene oxide-ethylene oxide block copolymers are sold under the trade names of Pluronic or Ploxamer). Compositions comprising copolymer micelles may be mixed with a viscoelastic polymer, such as hydroxypropylmethylcellulose, in order to maintain the structural integrity of the anterior chamber.

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The present invention further provides for compositions comprising a plurality of miotic, mydriatic and/or anesthetic agents, in any combination.

The amount of miotic or mydriatic agent present in the composition may be that amount which produces the desired therapeutic effect; that is to say, the desired pupil size for the desired period of time. Such amounts will vary between agents, but may readily be determined using the dose-response relationships known to

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the skilled artisan. The concentration of miotic or mydriatic agent may vary from 0.001 mg/ml to 20 mg/ml, and preferably from 0.025 mg/ml to 10 mg/ml. As one specific, nonlimiting example, where the miotic drug is acetylcholine chloride, a polymer/drug complex formulation may be prepared using a solution of acetylcholine chloride with acetylcholine hyaluronate, where the acetylcholine concentration may be 10 mg/ml and the osmolality may be adjusted to 305 mOsm/kg by mannitol. As another specific, nonlimiting example, where the miotic agent is pilocarpine hydrochloride, a polymer/drug complex formulation may be prepared using a solution of pilocarpine hydrochloride with pilocarpine hyaluronate, where the pilocarpine concentration may be 1 mg/ml and the osmolality may be adjusted to 305 mOsm/kg by mannitol. As yet another specific, nonlimiting example, using the mydriatic drug atropine sulfate, a solution of atropine hyaluronate containing atropine sulfate may be prepared where the atropine concentration may be 0.3 mg/ml and the osmolality may be adjusted to 305 mOsm/kg by mannitol. In each of the foregoing examples in this paragraph, the cationic drug may be mixed with the polymer-drug complex in sterile water and the osmolality may then be adjusted using the neutral agent mannitol.

The present invention provides for compositions that provide sustained release of anesthetic agents, as described above, in which release of the agent is mediated by ionic interactions between the viscoelastic polymer and anesthetic drug. The compositions also provide a means for maintaining the structural integrity of the anterior chamber of the eye.

In a fifth set of nonlimiting embodiments, the present invention provides for compositions in which the sustained release of anesthetic agent is achieved through ionic interactions between the anesthetic agent and the viscoelastic polymer. In particular embodiments, a composition may comprise an anionic viscoelastic polymer and a cationic anesthetic agent, in which the cationic agent of the composition, when placed in the eye, may be released by displacement with endogenous sodium or potassium ions, or other naturally occurring cations. In one specific, nonlimiting embodiment, the anionic viscoelastic polymer may be sodium hyaluronate, and the cationic agent may be lidocaine hydrochloride, where, in the preparation of the composition, sodium chloride is removed by using an excess of the

lidocaine hydrochloride in the presence of a lesser amount of sodium hyaluronate, followed by dialysis. This process may be repeated several times to prepare a high purity of lidocaine hyaluronate ionic complex. In another specific, nonlimiting embodiment, the anionic viscoelastic polymer may be sodium chondroitin sulfate, and the cationic agent may be the anesthetic, tetracaine hydrochloride, which may be combined by interacting sodium chondroitin sulfate with tetracaine hydrochloride, yielding tetracaine chondroitin sulfate ionic complex. In yet another specific, nonlimiting embodiment, an ion exchange interaction between sodium hyaluronate and proparacaine hydrochloride can be effected, yielding proparacaine hyaluronate ionic complex.

In a sixth, related set of nonlimiting embodiments, the present invention provides for compositions in which the sustained release of anesthetic agents is achieved through ionic acid-base interactions between the agent and the viscoelastic polymer. In particular embodiments, a composition may comprise an acidic viscoelastic polymer (in its free acid form) and a basic anesthetic agent (in its neutral amino form), in which case the composition, when placed in the eye, will provide a relatively slow release of the anesthetic agent by ionic displacement of the drug from existing cations. In one specific, nonlimiting embodiment, the acidic viscoelastic polymer acid may be hyaluronic acid, and the basic agent may be the neutral anesthetic agent, lidocaine. When these two compounds are combined by an acid-base interaction in the composition, the polymeric complex lidocaine hyaluronate may be formed. In another specific, nonlimiting embodiment, hyaluronic acid may be interacted with the basic anesthetic agent, proparacaine in water at a temperature range of 5 to 50°C (wherein the proparacaine becomes protonated by the polyacid and is rendered a salt of the viscoelastic polymer), followed by dialysis, filtration or ultrafiltration to remove unreacted Lidocaine. The resulting lidocaine hyaluronate composition may then, alternatively, either be sterilized and adjusted to the appropriate pH and osmolality for use (for example, and not by way of limitation, where the pH range is between about 6.8 and 7.8, preferably between 7.2 and 7.4, and the osmolality is 285 ± 55 mOsm/kg and preferably between 290 and 320 mOsm/kg), or may be recovered by drying in vacuo or by lyophilization. In yet another specific,

nonlimiting embodiment of the invention, hyaluronic acid may be interacted with the anesthetic agent, proparacaine, in aqueous solution, using an excess of proparacaine, followed by filtration and dialysis, yielding the ionic polymer complex, proparacaine hyaluronate.

5 In a nonlimiting example relating to the sustained release of the anesthetic agent, Figure 3 depicts three representative conditions using an aqueous humor turnover rate of 1.5 microliters per minute (Schoenwald, 1993, "Pharmacokinetics in Ocular Drug Delivery" (chapter 10) in Biopharmaceuticals of Ocular Drug Delivery, CRC Press, Inc., Boca Raton FL). Units for unbound
10 anesthetic are given in moles per liter, and units for viscoelastic polymers are given in units of equivalents per liter, which would describe combinations of any viscoelastic polymer with any anesthetic drug. Total initial concentration of anesthetic, utilizing lidocaine as an example, is 0.0085 mole/liter.

 Lidocaine has been reported to bind plasma at concentrations between
15 1 and 4 $\mu\text{g/ml}$ with 60-80% of lidocaine bound to protein (ASTRA Pharmaceutical Co. product information sheet, Xylocaine (lidocaine hydrochloride). Assuming that this binding is ionic in nature between the cationic lidocaine and anionic groups in the plasma, the calculated equilibrium constant would be 0.433 for binding of lidocaine to an anionic polymer.

20 In Figure 3, curve A represents unbound anesthetic, wherefor the initial concentration of 0.00850 mole/liter is diminished to 0.00143 mole/liter after 6 hours of dilution in the anterior chamber of the eye (with a total volume of 0.8 ml), caused by the turnover rate of aqueous humor. This is a decrease in lidocaine concentration of 83%.

25 Curve B of Figure 3 represents a combination of unbound lidocaine (no viscoelastic polymer present) and ion-complexed (bound) anesthetic-viscoelastic polymer complex. In this curve, the anesthetic-viscoelastic polymer complex has a calculated equilibrium constant of 0.433. From curve B it may be seen that, with an initial concentration of unbound anesthetic of 0.0490 mole/liter and a bound
30 anesthetic concentration of 0.150 equivalents/liter (producing an initial concentration of 0.00850 mole/liter of unbound lidocaine), at 6 hours of aqueous turnover, 0.00512

mole/liter of lidocaine remains in the anterior chamber. This is a decrease in lidocaine concentration of 40%. However, this final concentration is more than 3.6-fold greater than the final concentration of unbound drug observed after 6 hours.

Curve C of Figure 3 represents ion-complexed (bound) anesthetic-viscoelastic polymer using an equilibrium constant of 0.433, wherein the initial concentration of 0.348 equivalents/liter (producing an initial concentration of 0.0085 mole/liter of unbound lidocaine) is reduced to 0.00621 mole/liter of lidocaine after 6 hours of duration in the eye, caused by the turnover of aqueous humor. The final concentration represents a modest reduction in lidocaine concentration of 27% from its initial concentration. Additionally, the final lidocaine concentration from the anesthetic-polymer complex is more than 4.3 times greater than the final concentration of unbound anesthetic, and approximately 17% greater than that of the unbound anesthetic in the presence of the anesthetic-polymer complex (curve B).

Thus, from Figure 3 it may be seen that two conditions of ion-complexed anesthetic with viscoelastic polymer clearly demonstrate the effect of sustained release of anesthetic with time, as compared to unbound anesthetic, in the anterior chamber of the eye.

The present invention further provides for compositions comprising a plurality of anesthetic agents, and/or a plurality of viscoelastic polymers.

The amount of anesthetic agent present in the composition may be that in that amount which produces the desired therapeutic effect; that is to say, the desired level of anesthesia. Such amounts will vary between agents, but may readily be determined using the dose-response relationship known to the skilled artisan. The concentration of anesthetic agent may vary from 1 mg/ml to 50 mg/ml, and preferably from 5 mg/ml to 20 mg/ml. As one specific, nonlimiting example, where the anesthetic is lidocaine hydrochloride, an anesthetic-polymer complex formulation may be prepared using a solution of lidocaine hydrochloride with lidocaine hyaluronate, where the lidocaine concentration may be 20 mg/ml and the osmolality may be adjusted to 305 mOsm/kg by mannitol. As yet another specific, nonlimiting example, using the anesthetic agent tetracaine hydrochloride, an anesthetic-polymer complex formulation may be prepared using a solution of tetracaine hyaluronate

containing tetracaine hydrochloride, where the tetracaine concentration may be from 5 - 20 mg/ml and the osmolality may be adjusted to 305 mOsm/kg by mannitol. As yet another specific, nonlimiting example, using the anesthetic agent proparacaine, a solution of proparacaine hyaluronate containing proparacaine hydrochloride may be prepared where the proparacaine concentration may be from 5 - 20 mg/ml and the osmolality may be adjusted to 305 mOsm/kg by mannitol. In each of the foregoing examples in this paragraph, the cationic anesthetic agent may be mixed with the polymer-anesthetic drug complex in sterile water and the osmolality may then be adjusted using the neutral agent, mannitol. In yet a further specific, nonlimiting example, the anesthetic-polymer complex may be mixed with additional viscoelastic polymer solution, and the osmolality may be adjusted using the neutral agent, mannitol.

The present invention further provides for compositions that provide sustained release of anesthetic agents in combination with miotic or mydriatic agents. Specifically, the present invention comprises a viscoelastic polymer-anesthetic-miotic drug complex and a viscoelastic polymer-anesthetic-mydriatic drug complex in which release of the anesthetic agents and the drugs are mediated by ionic interactions between the viscoelastic polymer and the anesthetic agents and the miotic or mydriatic agents. Such compositions also provide a means for maintaining the structural integrity of the anterior chamber of the eye.

Because it is important, during ophthalmologic surgery, to maintain the osmolality of the anterior chamber of the eye, the compositions of the invention preferably exhibit an osmolality such that their introduction into the eye may not detrimentally alter the osmolality of the anterior chamber. The osmolality of the natural contents of the anterior chamber has been reported to be 301-305 mOsm/kg (Geigy Scientific Tables, Volume 1, Ed. C. Lentner, Eighth Edition, 1981, Basle, Switzerland). The osmolality of viscoelastic polymer drug ion complex could be maintained by excess drug in its salt form (for example, a 3.0% solution of phenylephrine chloride is isotonic in comparison to a 0.9 weight percent NaCl solution), or by a solution of, or in combination with, a neutral agent, such as glycerine (where a 2.6 weight percent solution is isotonic relative to a 0.9 weight

percent NaCl solution) or mannitol (where a 5.07% solution is isotonic relative to a 0.9 weight percent NaCl solution). If traditional isotonic solutions are used, which may contain sodium ions, potassium ions, calcium ions, etc., such ions may prematurely displace the ion-complexed drug, releasing it into solution, and an excess of the cationic drug may be required to be added in order to readjust the polymer-drug equilibrium. In preferred embodiments of the invention, the osmolality of the compositions may be between about 280 and 340 mOsm/kg, and preferably between about 280-340 mOsm/kg.

In order to maintain the structural integrity of the anterior chamber of the eye, the compositions of the invention must be sufficiently viscous such as to prevent the chamber from collapsing during surgical manipulation. The compositions should also, however, be sufficiently fluid to permit their introduction into the anterior chamber by injection or extrusion, as well as their removal (for example, by irrigation) at the conclusion of the surgical procedure. Accordingly, the viscosity of a composition according to the invention is between 1,000 and 60,000 centistokes and preferably between 2,500 and 40,000 centistokes. Where viscoelastic polymers are used, the concentrations of viscoelastic polymer are preferably between about 10 mg/ml and 30 mg/ml in aqueous (preferably isotonic) solution.

5.6. METHODS OF USING COMPOSITIONS OF THE INVENTION

The compositions of the invention are particularly useful when employed during a variety of ophthalmological surgical procedures, such as procedures desirably performed while the pupil is dilated, including intracapsular and extracapsular surgery and fistulizing procedures, and procedures desirably performed while the pupil is miotic, including anterior segment surgery, such as surgical separation of vitreo/corneal adhesions, separation of iris/corneal adhesions, and the placement of phakic refractive implants and secondary aphakic implants.

For example, and not by way of limitation, compositions comprising a mydriatic agent, according to the invention, may be used in standard extracapsular cataract surgery carried out under topical or retrobulbar anesthesia.

It should be noted that retrobulbar anesthesia tends to make the iris somewhat more sensitive to dilating or constricting drops (Starling's Law). The mydriatic composition of the invention may then be injected into the anterior chamber before and/or after an appropriate capsulotomy. Irrigation, aspiration, expression, or phacoemulsification of the cataract may then be performed. The implant may then be inserted, and residual mydriatic viscous material may be irrigated from the eye. In such procedures, the composition of the invention may aid the extraction of the lens and implant placement.

In another nonlimiting example, miotic compositions according to the invention may be used in standard myopic refractive implant placement procedures. After a paracentesis is carried out, the miotic composition may be injected into the anterior chamber. Then, an entrance incision may be made, the implant may be positioned, the wound may be sutured, and the viscous miotic composition may be irrigated from the eye.

The use of compositions of the invention offer a number of advantages. First, the present invention provides for a composition which may simultaneously provide both mechanical and pharmaceutical activities useful in ophthalmological surgery. Second, the compositions of the invention may be used to satisfy a long-felt need for a means for providing sustained release of miotic or mydriatic agents during surgery. Third, the compositions of the invention may prevent or reduce a rise in intraocular pressure which may be associated with the use of a viscoelastic solution which does not comprise a miotic agent. Fourth, the use of compositions of the invention may be used to prevent posterior or anterior synechias by keeping the pupil dilated during the immediate post-operative phase.

Moreover, during conventional surgery, with loss of the chamber and hypotony there is loss of iris tone and function. Since the viscous compositions of the invention maintain the chamber and some degree of intraocular pressure, and are in contact with the iris for a prolonged period of time, a reservoir effect is established so that chamber maintenance, enhanced iris tone and response and drug delivery are concurrently achieved. Further, particularly when miosis is desired, the long term effect of miotics may blunt the pressure elevatory potential of the viscoelastic.

In further non-limiting embodiment, viscoelastic polymer-anesthetic comprising compositions of the invention are particularly useful when employed in cataract surgery, glaucoma surgery, and other intraocular procedures. For example, topical anesthesia is employed to anesthetize the corneal and conjunctival surface. A
5 paracentesis is then carried out to permit slow drainage of the anterior chamber which is replaced by the viscoelastic polymer-anesthetic complex combination through the paracentesis site. The chamber is deepened to the desired level and the surgical procedure is initiated.

The various publications cited herein are hereby incorporated by
10 reference in their entireties.

CLAIMS

1. A composition for use in ophthalmologic surgery comprising a viscoelastic polymer and an effective amount of an anesthetic agent.
2. The composition of claim 1, wherein the viscoelastic polymer is acidic and the anesthetic agent is basic.
3. The composition of claim 1, wherein the viscoelastic polymer is anionic and the anesthetic agent is cationic.
4. The composition of claim 1, wherein the viscoelastic polymer and the anesthetic agent form a viscoelastic polymer-anesthetic complex.
5. A composition for use in ophthalmology surgery comprising a viscoelastic polymer, an anesthetic agent, and a drug, wherein the viscoelastic polymer, the anesthetic agent, and the drug form an ionic viscoelastic polymer-anesthetic-drug complex, wherein the drug is selected from the group consisting of miotic and mydriatic agents.
6. The composition of claim 5, wherein the miotic and mydriatic agents are selected from the group consisting of atropine, pilocarpine, phenylephrine, isopilocarpine, acetylcholine, atropine sulfate, pilocarpine hydrochloride, phenylephrine hydrochloride, acetylcholine chloride, pilocarpine hydrochloride, and isopilocarpine hydrochloride.
7. The composition of claim 1, wherein the viscoelastic polymer is selected from the group consisting of one or more of hyaluronic acid, chondroitin sulfate, dermatan sulfate, carboxymethylcellulose, heparan sulfate, heparin, keratan sulfate, carboxymethylhydroxyethylcellulose, cellulose sulfate, cellulose phosphate, carboxymethylguar, carboxymethylhydroxypropylguar, xanthan gum, gellan gum,

welan gum, rhamsan gum, agarose, alginates, furcellaran, pectins, gum arabic, gum tragacanth, carrageenans, starch phosphates, starch succinates, glycoaminoglycans, polysaccharides, polypeptides, and polymers and copolymers of acrylamide, N-vinylpyrrolidone, dimethylacrylamide, acrylic acid, methacrylic acid, maleic anhydride, vinylsulfonic acid, styrenecarboxylic acid, 2-acrylamido-2-methylpropanesulfonic acid, vinylphosphonic acid, and 2-methacryloyloxyethylsulfonic acid.

8. The composition of claim 5, wherein the viscoelastic polymer is selected from the group consisting of one or more of hyaluronic acid, chondroitin sulfate, dermatan sulfate, carboxymethylcellulose, heparan sulfate, heparin, keratan sulfate, carboxymethylhydroxyethylcellulose, cellulose sulfate, cellulose phosphate, carboxymethylguar, carboxymethylhydroxypropylguar, xanthan gum, gellan gum, welan gum, rhamsan gum, agarose, alginates, furcellaran, pectins, gum arabic, gum tragacanth, carrageenans, starch phosphates, starch succinates, glycoaminoglycans, polysaccharides, polypeptides, and polymers and copolymers of acrylamide, N-vinylpyrrolidone, dimethylacrylamide, acrylic acid, methacrylic acid, maleic anhydride, vinylsulfonic acid, styrenecarboxylic acid, 2-acrylamido-2-methylpropanesulfonic acid, vinylphosphonic acid, and 2-methacryloyloxyethylsulfonic acid.

9. The composition of claim 1, wherein the anesthetic agent is selected from the group consisting of lidocaine, proparacaine, tetracaine, phenacaine, naepaine, cocaine, betoxycaine, bupivacaine, butacaine, butanilicaine, butoxycaine, carticaine, cyclomethycaine, dibucaine, dimethocaine, etidocaine, formcaine, hexylcaine, hydroxytetracaine, leucinocaine, mepivacaine, meprylcaine, metabutoxycaine, myrtecaine, octacaine, orthocaine, oxethazine, parethoxycaine, piperocaine, piridocaine, pirilocaine, procaine, propanocaine, propipocaine, propoxycaine, pseudocaine, pyrrocaine, ropivacaine, tolylcaine, tricaine, and trimecaine.

10. The composition of claim 5, wherein the anesthetic agent is selected from the group consisting of lidocaine, proparacaine, tetracaine, phenacaine, naepaine, cocaine, betoxycaine, bupivacaine, butacaine, butanilcaine, butoxycaine, carticaine, cyclomethycaine, dibucaine, dimethocaine, etidocaine, formcaine, hexylcaine, hydroxytetracaine, leucinocaine, mepivacaine, meprylcaine, metabutoxycaine, myrtecaine, octacaine, orthocaine, oxethazine, parethoxycaine, piperocaine, piridocaine, pirilocaine, procaine, propanocaine, propipocaine, propoxycaine, pseudocaine, pyrrocaine, ropivacaine, tolylcaine, tricaine, and trimecaine.
11. The composition of claim 1 wherein the viscoelastic polymer is hyaluronic acid and the anesthetic agent is lidocaine.
12. The composition of claim 5 wherein the viscoelastic polymer is hyaluronic acid and the anesthetic agent is lidocaine.
13. The composition of claim 1, wherein the viscoelastic polymer is hyaluronic acid and the anesthetic agent is tetracaine.
14. The composition of claim 5, wherein the viscoelastic polymer is hyaluronic acid and the anesthetic agent is tetracaine.
15. The composition of claim 1, wherein the viscoelastic polymer is hyaluronic acid and the anesthetic agent is proparacaine.
16. The composition of claim 5, wherein the viscoelastic polymer is hyaluronic acid and the anesthetic agent is proparacaine.
17. The composition of claim 1, wherein the viscoelastic polymer is hyaluronic acid and the anesthetic agent is phenacaine.

18. The composition of claim 5, wherein the viscoelastic polymer is hyaluronic acid and the anesthetic agent is phenacaine.
19. The composition of claim 1, wherein the viscoelastic polymer is hyaluronic acid and the anesthetic agent is cocaine.
- 5 20. The composition of claim 5, wherein the viscoelastic polymer is hyaluronic acid and the anesthetic agent is cocaine.
21. The composition of claim 1, wherein the viscoelastic polymer is hyaluronic acid and the anesthetic agent is naepaine.
22. The composition of claim 5, wherein the viscoelastic polymer is
10 hyaluronic acid and the anesthetic agent is naepaine.
23. The composition of claim 1, wherein the viscoelastic polymer is sodium hyaluronate and the anesthetic agent is lidocaine hydrochloride.
24. The composition of claim 5, wherein the viscoelastic polymer is sodium hyaluronate and the anesthetic agent is lidocaine hydrochloride.
- 15 25. The composition of claim 1, wherein the viscoelastic polymer is sodium hyaluronate and the anesthetic agent is proparacaine hydrochloride.
26. The composition of claim 5, wherein the viscoelastic polymer is sodium hyaluronate and the anesthetic agent is proparacaine hydrochloride.
27. The composition of claim 1, wherein the viscoelastic polymer is
20 sodium hyaluronate and the anesthetic agent is phenacaine hydrochloride.

28. The composition of claim 5, wherein the viscoelastic polymer is sodium hyaluronate and the anesthetic agent is phenacaine hydrochloride.

29. The composition of claim 1, wherein the viscoelastic polymer is sodium hyaluronate and the anesthetic agent is cocaine hydrochloride.

5 30. The composition of claim 5, wherein the viscoelastic polymer is sodium hyaluronate and the anesthetic agent is cocaine hydrochloride.

31. The composition of claim 1, wherein the viscoelastic polymer is sodium hyaluronate and the anesthetic agent is naepaine hydrochloride.

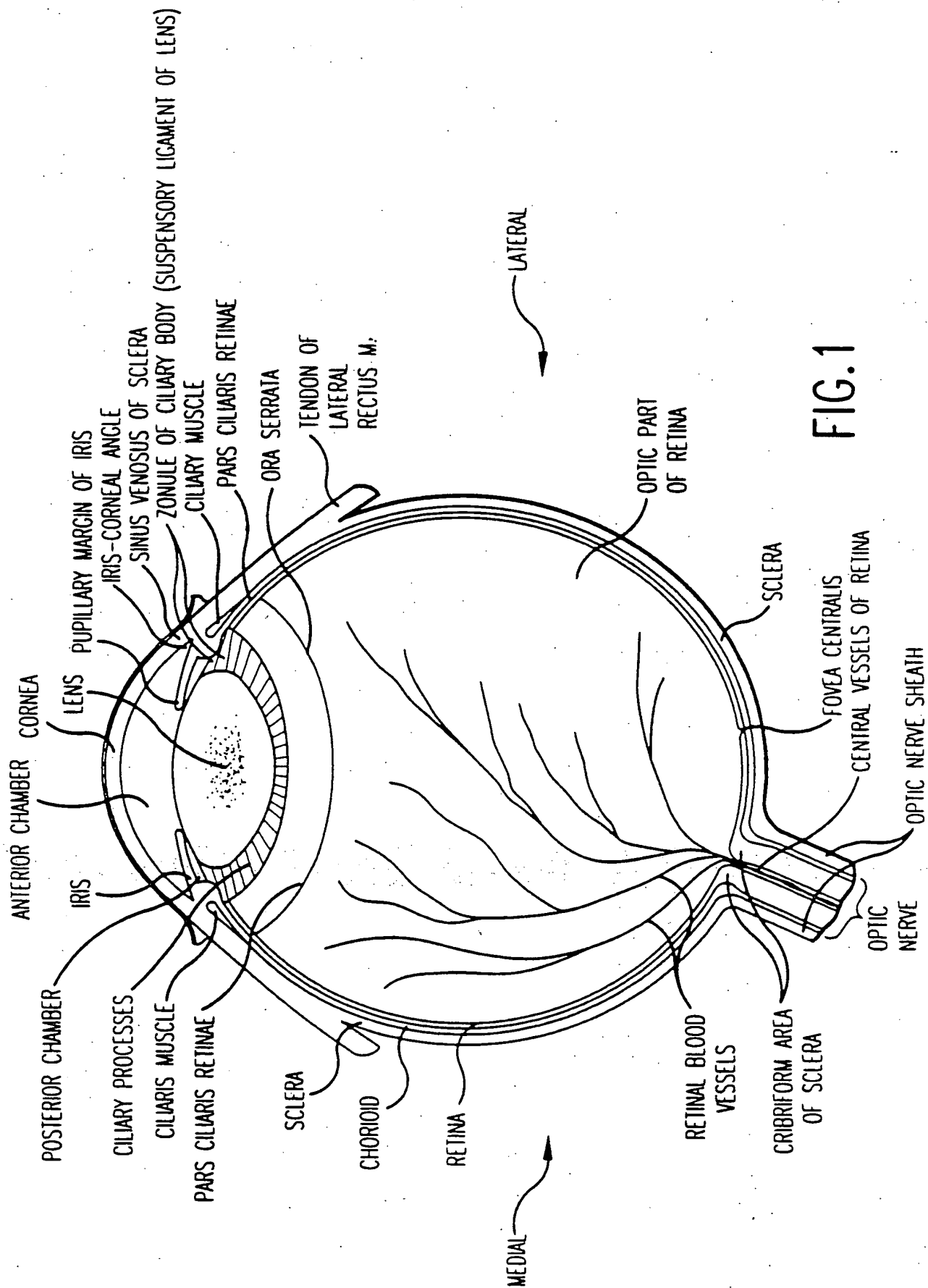
10 32. The composition of claim 1, wherein the viscoelastic polymer is sodium hyaluronate and the anesthetic agent is naepaine hydrochloride.

33. The composition of claim 5, wherein the complex is selected from the group consisting of atropine-lidocaine-hyaluronate, atropine-proparacaine-hyaluronate, atropine-tetracaine-hyaluronate, atropine-phenacaine-hyaluronate, atropine-cocaine-hyaluronate, atropine-naepaine-hyaluronate, atropine-lidocaine-
15 chondroitin sulfate, atropine-proparacaine-chondroitin sulfate, atropine-tetracaine-chondroitin sulfate, atropine-phenacaine-chondroitin sulfate, and atropine-naepaine-chondroitin sulfate.

34. The composition of claim 5, wherein the complex is selected from the group consisting of acetylcholine-lidocaine-hyaluronate, acetylcholine-proparacaine-hyaluronate, acetylcholine-tetracaine-hyaluronate, acetylcholine-phenacaine--
20 hyaluronate, acetylcholine-cocaine-hyaluronate, acetylcholine-naepaine-hyaluronate, acetylcholine-lidocaine-chondroitin sulfate, acetylcholine-proparacaine-chondroitin sulfate, acetylcholine-tetracaine-chondroitin sulfate, acetylcholine-phenacaine-chondroitin sulfate, and acetylcholine-naepaine-chondroitin sulfate.

35. The composition of claim 5, wherein the complex is selected from the group consisting of pilocarpine-lidocaine-hyaluronate, pilocarpine-proparacaine-hyaluronate, pilocarpine-tetracaine-hyaluronate, pilocarpine-phenacaine-hyaluronate, pilocarpine-cocaine-hyaluronate, pilocarpine-naepaine-hyaluronate, pilocarpine-
5 lidocaine-chondroitin sulfate, pilocarpine-proparacaine-chondroitin sulfate, pilocarpine-tetracaine-chondroitin sulfate, pilocarpine-phenacaine-chondroitin sulfate, and pilocarpine-naepaine-chondroitin sulfate.

36. A method of maintaining the structural integrity of the anterior
10 chamber of the eye during surgery while concurrently providing anesthesia, comprising administering a viscoelastic polymer and a therapeutically effective amount of an anesthetic agent to be administered to a subject in need thereof.



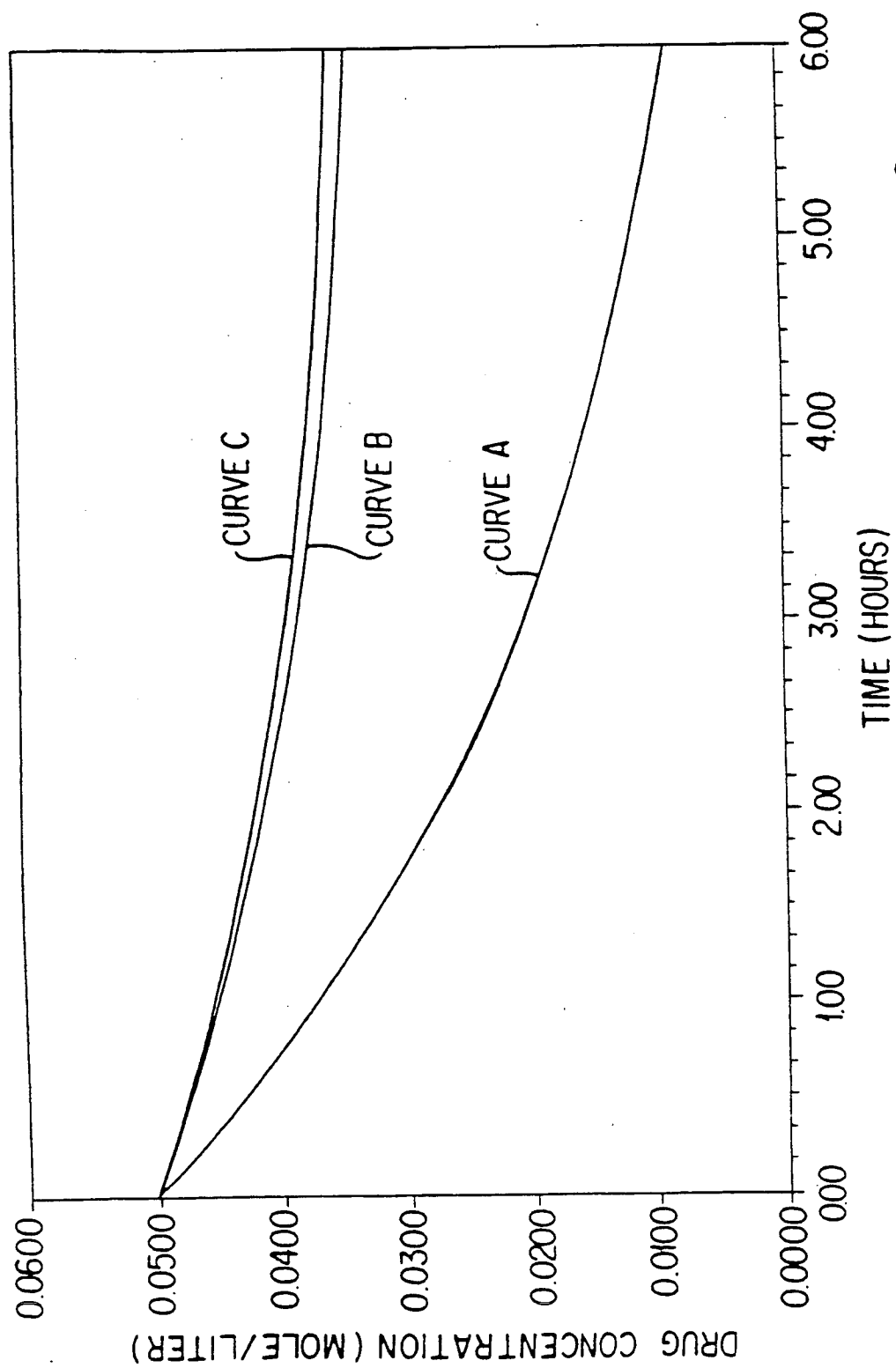


FIG. 2

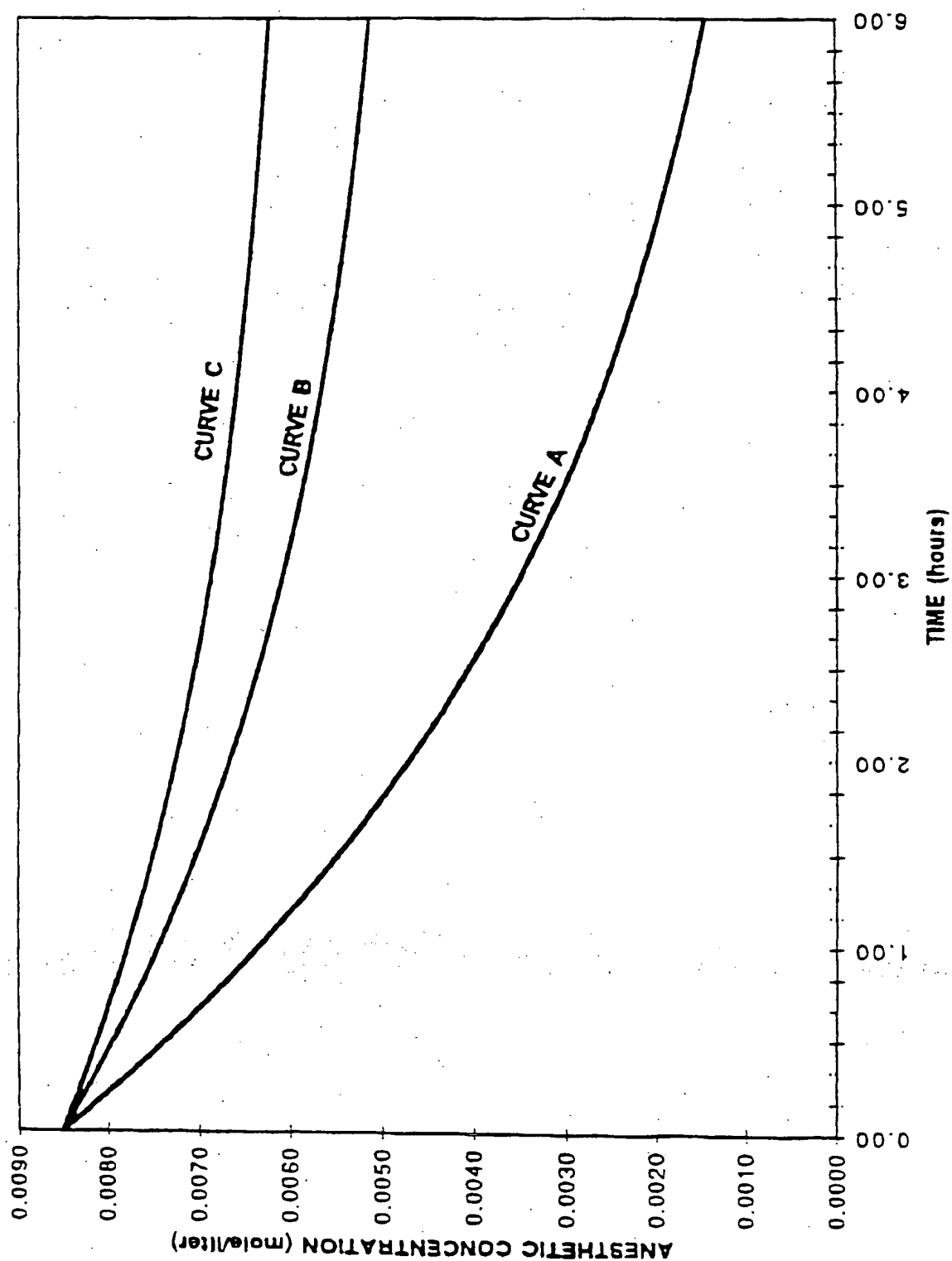


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/05320

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : 424/427, 428

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/427, 428

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHAN ET AL, Liquid Topical Ophthalmic or Injectable anaesthetic Comprises Rodocaine or Its Pharmaceutically Acceptable Salt, Chemical Abstracts, AN 89-272270, Abstract Only.	1-36

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

27 APRIL 1998

Date of mailing of the international search report

17 JUL 1998

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Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

CARLOS AZPURU

Telephone No. (703) 308-2351

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/05320

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61F 2/14

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